I. REMARKS

Upon entry of the above amendment, claims 1-10, 12-20 and 43-47 will be pending in the present application. In this amendment, claims 11 and 21 have been canceled without prejudice to or disclaimer of the subject matter contained therein. Claims 22-42 were previously cancelled. Claim 47 has been added.

Claim 1 has been amended to recite "A method for treating a respiratory disease in a patient while reducing or avoiding systemic side effects associated with inhaled or intranasal corticosteroids in said patient, which patient is a child and the method comprises administering to the patient a dose of a composition containing ciclesonide as the sole active ingredient, or a pharmaceutically acceptable salt thereof, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 µg, and wherein ciclesonide consists essentially of its R-epimer."

Basis may be found in the instant specification at page 2, lines 7-9, and the paragraph bridging pages 2-3, for the phrase "while reducing or avoiding systemic side effects associated with inhaled or intranasal corticosteroids in said patient". Basis may be found in previously pending claim 21 and in the instant specification on page 2, 5th line from the bottom, for the phrase "and wherein ciclesonide consists essentially of its R-epimer".

Basis for new claim 47 may be found in the instant specification in the paragraph bridging pages 2 and 3.

Therefore, no new matter is presented and entry of the amendments is

respectfully requested.

II. REJECTIONS UNDER 35 USC § 103(a)

A. REJECTION OF CLAIMS 1-16, 19, 20, 43 AND 44-46

At page 3 of the Official Action, the Examiner has rejected claims 1-16, 19, 20, 43 and 44-46 under 35 USC § 103(a) as being unpatentable over Oliver et al. (US Patent No. 6,120,752).

RESPONSE

The rejection is respectfully traversed. The Examiner has not established a prima facie case of obviousness against the presently pending claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some motivation or teaching in the references cited by the Examiner to combine the separate elements taught in the separate references. As the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to identify a reason that would have prompted a person

of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does... because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *See KSR International Co. v. Teleflex Inc. et al.*, 550 U.S. 398 at 417-418. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

The Examiner has failed to satisfy even one of these requirements in his rejection of the presently rejected claims.

Presently pending claim 1 is directed to a method for treating a respiratory disease in a patient while reducing or avoiding systemic side effects associated with inhaled or intranasal corticosteroids in said patient, which patient is a child and the method comprises administering to the patient a dose of a composition containing ciclesonide as the sole active ingredient, or a pharmaceutically acceptable salt thereof, wherein the dose of the composition comprises ciclesonide in an amount of from 20 to 200 μg, and wherein ciclesonide consists essentially of R-epimer."

As conceded by the Examiner at page 3, the Oliver et al. reference "does not anticipate wherein the patient is a child between the ages of 6 to 12 years."

However, the Examiner alleges that "Oliver et al. does make the treatment of such patients obvious." Applicants respectfully traverse. In view of the Examiner's statement that Oliver et al. does not contain any teaching regarding child patients and further in view of the amendments to the claims presented herein, it is quite clear that the Oliver et al. reference does not "teach or suggest all the limitations of the claims" as required by *In re Wilson*, supra.

In his rejection, the Examiner states on page 4 that "[i]t would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the inhalation composition taught by Oliver et al. in patients who are children between the ages of 6 to 12 years. One would have been motivated to do so because Oliver et al. is silent as to the age of the patient receiving the composition, therefore one of ordinary skill in the art would expect that administration of Oliver et al.'s composition to patients of any age would work equally well in treating asthma."

Applicants take issue with this assertion. In view of the adverse events (AEs) associated with corticosteroids, applicants respectfully submit that it would not be obvious for a person of ordinary skill to assume that effectiveness of a corticosteroid in an adult population would necessarily translate to effectiveness and safety in a pediatric population.

It is well known in the art that certain corticosteroids have adverse events (AEs), particularly at high dosages. As reported in Derom et al. "*Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and airway*

responsiveness to adenosine 5'monophosphate in asthmatic patients", Pulm. Pharmacol. Ther., 2005, 18:328-36, (cited herewith in an Information Disclosure Statement), potential long-term adverse effects of inhaled glucocorticosteroids include: growth reduction, decreased bone mineral density, increased risk of bone fractures, thinning of the skin, easy bruising and cataracts (see page 328, col. 2). Other potential AEs include hypothalamic-pituitary-adrenal (HPA) axis suppression and local oropharyngeal AEs such as oral candidiasis as reported by Gelfand et al. in "*Once daily ciclesonide in children: efficacy and safety in asthma*", J. Pediatr. 2006, 148:377-383 (cited herewith in an Information Disclosure Statement). (See page 377, paragraph 1).

Gelfand et al. teach at page 377 that, despite the fact that "[c]urrent guidelines for childhood asthma recommend early intervention with inhaled corticosteroids (ICS) to control symptoms, improve lung function and prevent exacerbations", "many children do not receive ICS therapy, because of concerns about adverse events". Gelfand et al. also teach at page 377 that "an effective ICS, with a simplified dosing regimen and a more favorable safety profile (than other inhaled corticosteroids) may increase adherence in children and thus improve the benefits in this population."

It is clear, therefore, that different patient populations may be impacted by adverse events in different ways. For example, in pediatric populations that are prescribed inhaled corticosteroids, there is particular concern regarding the possible

effects of the ICS on the patients' long term growth; specifically, children that inhale corticosteroids can suffer from retarded bone development which may result in the patient not reaching their potential height by adult age. Such an adverse effect is obviously not of particular concern to adult patients as they have most likely finished growing.

Accordingly, a person of ordinary skill in the art, upon reading a reference that discloses a certain corticosteroid which is silent regarding the treatment population, would not simplistically assume that the corticosteroid disclosed will "work equally well" in any patient based on an absence of teaching regarding the patient population. Instead, a person of ordinary skill in the art would be aware of the potential adverse events known to be associated with inhaled corticosteroids. As such, a person of ordinary skill would know that the adverse events that can affect a targeted patient population must be considered. Consideration of this "background knowledge possessed by a person having ordinary skill in the art" is required by *KSR*, supra, and is clearly lacking in the Examiner's rejection.

Further, "the proposed modification of the prior art" by the Examiner "must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made" as required by *Amgen*, supra. Based on the potential adverse events associated with inhaled corticosteroids, a person of ordinary skill would not have a reasonable expectation of success to use a previously known inhaled corticosteroid in any patient

population without investigating the adverse events that might occur in those patient populations.

Accordingly, applicants respectfully submit that administering a corticosteroid active ingredient taught in the prior art (but with no mention of the patient population) to a targeted patient population would not be an obvious endeavor as alleged by the Examiner.

Therefore, applicants invite the Examiner to review the findings disclosed in several references cited herewith in an Information Disclosure Statement:

1) von Berg, et al., *"Comparison of the efficacy and safety of ciclesonide 160µg once daily vs. budesonide 400µg once daily in children with asthma"*, Pediatr Allergy Immunol 2007:18: 391-400;
2) Agertoft, et al., *"Lower leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate"*, Pediatr Allergy Immunol 2009;
3) Agertoft, et al. *"Short term lower-leg growth and urine cortisol excretion in children treated with ciclesonide"*, J Allergy Clin Immunol 2005; 115:940-5; and
4) Skoner, et al. *"Assessment of the Long-term Safety of Inhaled Ciclesonide on Growth in Children With Asthma"*, Pediatrics, vol. 121, No. 1, January, 2008.

In these references, the superiority of ciclesonide with regards to adverse events when compared to other inhaled corticosteroids is absolutely clear.

First, von Berg, et al. compared the safety and efficacy of ciclesonide and budesonide in children and found that "in children treated with ciclesonide there was significantly less reduction in body height and suppression of 24-h urinary cortisol excretion compared with children treated with budesonide after 12 [weeks]". *See* von Berg, et al., Abstract, page 391. Ciclesonide was administered via a hydrofluoroalkane metered-dose-inhaler at a dosage of 160µg, while budesonide was administered via a dry powder Pulmicort Turbohaler at a dosage of 400µg. While the administration formulations for delivering the active ingredients ciclesonide and budesoide were different, both administration formulations (metered dose inhalers and dry powders) are well known in the art.

von Berg, et al. noted on page 396, col. 2, that "[t]he increase in body height was significantly greater in ciclesonide-treated patients than in budesonide-treated patients". Importantly, von Berg, et al. noted that the body height difference between the ciclesonide and budesonide groups was 0.481 cm over 12 weeks. Figure 2 on page 397 contains a graphical representation of the observed changes in body height in the respective groups.

von Berg, et al. at page 398, col. 2, go on to state, in relevant part:

> "Previous studies investigating the effect of treatment with budesonide on children have shown significant reductions in body height compared with placebo, with the greatest reduction occurring during the first year of treatment.

> In a previous placebo-controlled study, ciclesonide 40, 80 or 160 µg once daily was shown not to affect short-term lower leg growth rate in children, as assessed by knemometry...as well as 1-yr. growth velocity. The results of these studies conducted on childhood growth cannot be used to predict growth during long-term treatment. They are, however, suitable for comparing the growth-inhibiting effects of individual inhaled steroids.
>
> The differences in body height and urinary cortisol excretion between treatments may indicate a favorable systemic safety profile of ciclesonide compared with budesonide."

The Agertoft, et al. reference entitled *"Lower leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate"* found that ciclesonide "had no significant effect on lower-leg growth rate in children aged 6-12 [years] with mild asthma", but "[i]n contrast, a similar dose of [fluticasone propionate] significantly reduced lower-leg growth rate compared with placebo and [ciclesonide]". *See* Abstract, page 1. Both ciclesonide and fluticasone propionate were administered by way of a pressurized metered dose inhaler (MDI) with hydrofluoroalkane 134-a as the propellant. In particular, Agertoft, et al. found that "[e]fficacy studies have suggested that µg for µg, [ciclesonide] and [fluticasone propionate] are equally effective in children ... as well as in adults." However, when the systemic effects were assessed after administration to pre-pubertal children, ciclesonide at a dosage of "320 µg was associated with significantly less negative impact on lower-leg growth rate ... than a similar dose of [fluticasone propionate], indicating that the systemic effects of these two drugs are different."

Further, the Agertoft et al. reference entitled *"Short term lower-leg growth and*

urine cortisol excretion in children treated with ciclesonide" compared the lower-leg growth effects of three separate dosages (40μg, 80μg and 160μg) of ciclesonide with placebo and found that "[n]o statistically significant differences were seen in lower-leg growth rates between any of the ciclesonide treatments and placebo." *See* Abstract, page 940.

Skoner, et al. confirmed these superior properties of ciclesonide in the reference *"Assessment of the Long-term Safety of Inhaled Ciclesonide on Growth in Children With Asthma"*. In a study of 661 patients, "[c]iclesonide was noninferior to placebo with respect to growth, showing no detectable effect on the 1-year growth rate of children with mild, persistent asthma." *See* page e6, col. 2.

Therefore, because ciclesonide may have a more favorable safety profile than the inhaled corticosteroids fluticasone propionate and budesonide which exhibit adverse effects in children, administration of ciclesonide to pediatric patients may result in a reduced occurrence of adverse effects as compared to administration of other inhaled corticosteroids.

Accordingly, the Examiner has not satisfied even one of the three requirements for establishing a prima facie case of obviousness. Therefore, the presently claimed methods of treating a respiratory disease in a child with ciclesonide are not obvious over the disclosure contained in Oliver et al. which is silent regarding the treatment population. Withdrawal of this rejection is respectfully requested.

B. REJECTION OF CLAIMS 1-13 AND 17-21

At page 4 of the Official Action, the Examiner has rejected claims 1-13 and 17-21 under 35 USC § 103(a) as being unpatentable over Calatayud et al. (UK Patent Application GB 2247680).

RESPONSE

The rejection is respectfully traversed. The Examiner has not established a prima facie case of obviousness against the presently pending claims.

The requirements for establishing a prima facie case of obviousness are outlined above in section II. A., and for the sake of brevity, applicants incorporate by reference these requirements into the present discussion of the Calatayud et al. reference.

Similar to the Examiner's rejection of the claims based on the disclosure of Oliver et al., the Examiner has also failed to satisfy even one of the three requirements for establishing a prima facie case of obviousness in the present rejection of claims 1-13 and 17-21 over the disclosure of Calatayud et al.

First, the Examiner concedes at page 5, 2nd paragraph of the Official Action that "Calatayud et al. does not anticipate wherein the patient is a child between the ages of 6 to 12 years." However, the Examiner alleges that "Calatayud et al. does make the treatment of such patients obvious." Therefore, the Calatayud et al. reference does not "teach or suggest all the limitations of the claims" as required by *In re Wilson*, supra.

In his rejection, the Examiner states on page 5 that "[i]t would have been obvious to one of ordinary skill in the art at the time of the instant invention to use the inhalation composition taught by Calatayud et al. in patients who are children between the ages of 6 to 12 years. One would have been motivated to do so because Calatayud et al. is silent as to the age of the patient receiving the composition, therefore one of ordinary skill in the art would expect that administration of Calatayud et al.'s composition to patients of any age would work equally well in treating asthma."

Applicants again take issue with this assertion for the same reasons as outlined above in section II. A. Applicants respectfully submit that, in view of the adverse events (AEs) associated with corticosteroids it would not be obvious for a person of ordinary skill to assume that effectiveness of a corticosteroid in an adult population would necessarily translate to effectiveness and safety in a pediatric population.

In the present rejection of claims 1-13 and 17-21, the Examiner has again made the simplistic assertion that a person of ordinary skill in the art would, upon reading a reference that discloses a previously known corticosteroid but is silent regarding the patient population, assume that the previously known corticosteroid will "work equally well" in any patient population. However, as stated above in section II. A., a person of ordinary skill in the art would indeed be aware of the potential adverse events known to be associated with inhaled corticosteroids. As

such, a person of ordinary skill would know that the adverse events that can affect the targeted patient population must be considered. Consideration of this "background knowledge possessed by a person having ordinary skill in the art" is required by *KSR*, supra, and is clearly lacking in the Examiner's rejection.

Further, as stated above in section II. A., "the proposed modification of the prior art" by the Examiner "must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made" as required by *Amgen*, supra. Based on the potential adverse events associated with inhaled corticosteroids, a person of ordinary skill would not have a reasonable expectation of success to use a previously known inhaled corticosteroid in any patient population without investigating the adverse events that might occur in those patient populations.

Accordingly, applicants respectfully submit that the administration of a corticosteroid active ingredient that was taught in the prior art (but with no mention of the patient population) would not be an obvious endeavor as alleged by the Examiner.

In view of the teachings of the references discussed above in section II. A. in great detail, ciclesonide may have a more favorable safety profile than fluticasone propionate and budesonide which exhibit adverse effects in children, As such, administration of ciclesonide to pediatric patients may result in a reduced occurrence of adverse effects as compared to administration of other inhaled

corticosteroids.

Accordingly, the Examiner has not satisfied even one of the three requirements for establishing a prima facie case of obviousness. Therefore, the presently claimed methods of treating a respiratory disease in a child with ciclesonide are not obvious over the disclosure contained in Calatayud et al. which is silent regarding the treatment population. Withdrawal of this rejection is respectfully requested.

III. CONCLUSION

Applicants assert that the claims are in condition for immediate allowance and early notice to that effect is earnestly solicited. Should the Examiner deem that any further action by Applicants' undersigned representative is desirable and/or necessary, the Examiner is invited to telephone the undersigned at the number set forth below.

Applicants authorize the Director to charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP

Joshua B. Goldberg
Registration No. 44,126
Sheldon M. McGee
Registration No. 50,454
Customer No. 34375

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THE NATH LAW GROUP
112 South West Street
Alexandria, Virginia 22314
Tel: (703) 548-6284
Fax: (703) 683-8396
JBG/SMM/ROA2.final.doc